PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2007/007854	29.03.2007	29.03.2006

International Patent Classification (IPC) or both national classification and IPC
INV. C07D233/86 C07D235/02 A61K31/4166 A61K31/4184 A61P35/00

Applicant
THE REGENTS OF THE UNIVERSITY OF CALIFORNIA

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Moriggi, J Telephone No. +49 89 2399-2692

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2007/007854

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☒ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in electronic form.

      ☐ furnished subsequently to this Authority for the purposes of search.

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 10-24, 32-40, 42-48

because:

☒ the said international application, or the said claims Nos. 10-24, 42-48 relate to the following subject matter which does not require an international search *(specify)*:

see separate sheet

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 32-40, 42, 45-48 are so unclear that no meaningful opinion could be formed *(specify)*:

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☐ no international search report has been established for the whole application or for said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-48
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-48
Industrial applicability (IA)	Yes:	Claims	1-48
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Re Item III.
Claims 10-24 and 42-48 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv) PCT.

In addition, present claims 32, 42, and 48 relate to methods which has a given desired property or effect, namely selecting a compound or interfering with mRNA transcription or preventing transnuclear dislocation. However, contrary to the requirements of clarity of Article 6 PCT, a result-to-be-achieved type of definition does not allow the scope of the claim to be ascertained. The fact that any compound could be screened does not overcome this objection, as the skilled person would not have knowledge beforehand as to whether it would fall within the scope claimed, except for the compounds disclosed in the present description. Undue experimentation would be required to screen compounds randomly.

The search of claims 32, 42, and 48 was consequently restricted to compounds falling within the formula disclosed in claim 1.

Re Item V.
As previously mentioned, claims 10-24 and 42-48 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv) PCT. The patentability is dependent upon the wording of the claims. The EPO, for example, does not recognise as patentable the subject-matter of claims to the use of a compound in medical treatment but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment. Nevertheless, an opinion will be given.

1. Reference
Reference is made to the following document:

D1: FR 2 693 461

2. Novelty
There is an overlap between the general formula of claim 1 of the present application, wherein R_1 and R_2 are methyl and R_3 is cyano and formula (I) of claim 1 of prior art document D1, wherein R_1 is cyano, R_2 is trifluoromethyl, X is a sulfur atom, and R_3 is aryl substituted by cyano or by halogen and cyano.

As far as overlapping chemical formulae are concerned, novelty is acknowledged if the

claimed subject-matter is distinguished from the prior art in the range of overlap by a new technical element. The fact that the general formula of claim 1 of the present application shows a phenyl group (as opposed to an unspecified aryl group in D1) can be seen as such a new technical teaching. Novelty of the claims 1-9 can therefore be acknowledged. A similar reasoning applies to the other claims.

As a result, the subject matter of the present application appears to be novel in the sense of Article 33(2) PCT.

3. Inventive Step

Prior art document D1, which can be considered to represent the most relevant state of the art, discloses diarylthiohydantoin derivatives useful in the treatment of prostate cancer. As previously mentioned, there is a structural overlap between the compounds of the present application and the compounds of D1. Thus, the basic chemical structure according to the chemical formula of claim 1 is already known from D1 to have the claimed anti-cancer activity.

Therefore, the problem underlying the present application can not be simply seen as how to provide further diarylthiohydantoin derivatives useful in the treatment of prostate cancer - the solution consisting in the compounds of claim 1 of the present application would appear as an obvious solution to the person skilled in the art - but as how to provide further diarylthiohydantoin derivatives useful in the treatment of prostate cancer that possess unexpected properties over the prior art.

The data provided in the present application (paragraph 119, tables 1 and 4) seem to indicate that at least some of the compounds falling within the general formula of claim 1 of the present application actually possess the claimed activity.

However, a comparative test between the compounds of the present application and those disclosed in the prior art or any other appropriate information are missing. In the absence of any such results or arguments, it cannot be decided whether the compounds of claim 1 of the present application actually solve the aforementioned technical problem.

As a consequence, the subject matter of claims 1-24 and 32-48 of the present application according to the first invention cannot be considered as involving an inventive step in the sense of Article 33(3) PCT. The same reasoning applies to the

subject-matter of all the other claims, which therefore are also considered not inventive.

It is emphasised that only the compounds that exhibit an unexpected effect can be claimed. In other words, the unexpected effect has to be present over the entire domain covered by the claimed compounds. It also is reminded that the breadth of the claims should be such that every compound falling within the scope of the claims actually provides a solution to the problem underlying the invention. As a consequence, the term "alkyl" (alone or in combination with other chemical residues), used throughout the claims and without further definition, is open ended, thereby comprising subject-matter which is inherently likely not to solve the relevant technical problem. As chemical species can be precisely defined by the number of atoms involved, the incorporation of the specific substituents is necessary.

Favourable data or any appropriate information that could support an inventive step and demonstrate that the compounds disclosed in present claim 1 actually provide a solution to the aforementioned technical problem are missing. It is reminded that, in the absence of a specific aim, the provision of compounds, even if novel, is merely considered as an enrichment of chemistry and thus can not be seen as involving an inventive step in the sense of Article 33(3) PCT. In other words, in the absence of any inventive step associated with the final compounds obtained through the process disclosed in claim 25, said process can not be seen as involving an inventive step.

The subject matter of the claims 25-31 does not involve an inventive step in the sense of Article 33(3) PCT.

4. Industrial Applicability

The subject-matter of claims 1-48 appears to be industrially applicable in the sense of Article 33(4) PCT.

Remarks

Several examples of the description do not fall within the scope of the claims. This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear (Article 6 PCT). In particular, example 58 (also named NC56 or formula 49), which is the subject matter of claim 8, does not fall within the scope of claim 1 because the definition of R_3 does not include a dialkylcarbamoyl alkyl.

Additionally, in order to meet the requirements of Rule 6.4 PCT, claims 32, 42, and 48 should be made dependent on claim 1.

Re Item VI.

Prior art document WO 2006/124118, cited in the International Search Report, could become relevant at a later stage.